Generic Prices Take Flight

The FDA Is Struggling to Ground Them

Stephen Barlas

Over the past few years, safety and effectiveness have been the issues plaguing generic pharmaceuticals. But concern has largely faded about the quality of active pharmaceutical ingredients manufactured in places such as India or China, or the bioequivalence of products such as Budeprion XL 300 mg. Now a new series of question marks hovers over generic drugs.

The price of generics looms largest. Still prized for their low cost, some generics have lifted off into the dollar stratosphere—though admittedly they haven't reached the moon like some new brand-name drugs, such as Gilead's Sovaldi. That said, the number of generics posting higher prices, and the height of those leaps, worry consumers, payers, and some members of Congress.

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A variety of reasons account for the increases. Loss of momentary competition in a category because one manufacturer stops producing, for any number of reasons, comes into play. So does the dropping of product lines. New products in existing generic markets find the door to entry barred, sometimes by competitors already selling into that market, sometimes by a Food and Drug Administration (FDA) besieged by applications and understaffed to handle them.

The FDA must approve abbreviated new drug applications (ANDAs) filed by generic drug companies, and the agency was thought to be making big strides in light of $300 million a year in new user fees from generic companies thanks to the 2012 Generic Drug User Fee Amendments (GDUFA). The fees were supposed to guarantee faster approval, leading to lower costs to companies and lower prices for new drugs that would be introduced more quickly.[1] But some industry experts think that GDUFA has failed to deliver, and that the FDA has gone backward on approval speed.

Walter Jump, President of Cornerstone Regulatory (a consulting firm that works with both generic and brand-name companies), says that costs for industry have increased since the passage of GDUFA. "Nothing provided for in GDUFA will decrease costs to industry. Although the Generic Drug User Fee Amendments propose to reduce the current delays in the drug approval process, currently there is no proof that the delays in the current approval process are being addressed," Jump says. In fact, the FDA's ANDA backlog has increased. Currently, Mylan Inc. has 288 ANDAs awaiting FDA approval that represent $111.5 billion in annual brand sales, according to IMS Health. Forty-three of these pending ANDAs are potential first-to-file opportunities, representing $28.7 billion in annual brand sales for the 12 months ending June 30, 2014, IMS Health adds.

During a meeting at the FDA on September 17, 2014, called to air a number of GDUFA issues, David R. Gaugh, RPh, Senior Vice President for Sciences and Regulatory Affairs of the Generic Pharmaceutical Association (GPhA), said that in 2013, the median time for generic drug approvals jumped to 36 months and is projected to reach 43 months in 2014 once the final numbers are in.

Jump hypothesizes that the slowdown in approval times may be related in part to the need for more-experienced FDA drug reviewers to spend part of their time training new drug reviewers who have been hired thanks to the $300 million infusion. Such training will take time to ensure that all these new employees are consistent in their reviews.

"The generic supply chain has become very fragile. For many generic drugs, there are only a few suppliers," says Adam J. Fein, PhD, of Pembroke Consulting, Inc. "Any supply shock to the system, such as a manufacturing problem or FDA action, can rapidly create a shortage because alternative capacity isn't ramping up to meet demand."

Tetracycline shortages, for instance, have resulted in much higher generic prices. Watson Pharmaceuticals stopped producing tetracycline tablets in December 2013 and was acquired by Activis PLC in 2014. Activis has not restarted production. As of October 2014, Teva Pharmaceutical Industries Ltd., a one-time producer of tetracycline, was no longer selling the product because of a raw material shortage. Heritage Pharmaceuticals Inc. markets the brand-name version of tetracycline, called Achromycin V. In October 2013, Heritage announced it was making available generic tetracycline HCl capsules in 250- and 500-mg strengths. Not surprisingly, then, with only one manufacturer in the game, the price of tetracycline 500-mg and 250-mg tablets increased from $0.05 and $0.06 per capsule in July 2013 to $8.59 and $4.26 in July 2014. Those are increases of 17,714% and 7,340%, based on pricing data from Drug Channels, a website written by Dr. Fein.[2]

The Importance of Generics

The importance of generics to slowing the growth of health care costs is obvious. The FDA has approved more than 8,000 generic equivalents to brand-name drugs; as a result, generics represent more than 85% of all U.S. prescriptions and have saved U.S. consumers and the health care system $1.5 trillion in the past decade alone, according to the GPhA.

For years, the discounted price of generics was the glittering jewel in their crown. Not any more. Escalating prices have hit hospital pharmacies, drug stores, and consumers alike. This year, Walgreens fired its chief financial officer and the president of its pharmacy, health, and wellness division because they underestimated the cost of generic drugs and overestimated pharmacy unit earnings for the fiscal year ending in 2016.

Insurance plans are responding in order to mitigate the price pressures. Dr. Fein states, "Some payers are already establishing a 'nonpreferred' or 'more costly' generic tier for products that

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have experienced significant inflation. If generic inflation continues, I expect to see more plans with multiple generic tiers."

Hospitals are suffering from generic drug price increases, too, since drug costs for any inpatient "event" are bundled into the cost of reimbursement for that patient, whether Medicare, Medicaid, or a private insurer is paying. Any generic drug price increase will not be reflected in the global payment from private or public insurers, paid on the basis of a diagnosis-related group (DRG)—at least not any time soon. True, generic costs make up a tiny percentage of any DRG reimbursement. But over the course of a year, they may add up. Hospitals also face potential cost implications on the outpatient pharmacy side. "The average selling price for the generic will not be updated for up to six months after the actual price increase, meaning hospitals will have to pay the difference for that six-month period," explains Bill Woodward, MS, RPh, Senior Director of Pharmacy Contracting for Novation, a contracting and information company that serves 100,000 members and affiliates of VHA Inc. and UHC, two national health care alliances; Children's Hospital Association, an alliance of the nation's leading pediatric facilities; and Provista, LLC.

Generic price increases have caught the attention of some in Congress. On October 2, Representative Elijah Cummings, ranking member of the House Committee on Oversight and Government Reform, and Senator Bernard Sanders, Chairman of the Subcommittee on Primary Health and Aging of the Senate Committee on Health, Education, Labor, and Pensions, sent letters to 14 generic drug manufacturers requesting information about the escalating prices they have been charging for generic drugs.[3] "When you see how much the prices of these drugs have increased just over the past year, it's staggering, and we want to know why," says Cummings.

Huge Generic Price Increases

In their letters, Cummings and Sanders cited data from the Healthcare Supply Chain Association on purchases of 10 generic drugs by group purchasing organizations for which prices have skyrocketed in the past year. Among the citations:

- Albuterol sulfate, used to treat asthma and other lung conditions, increased 4,014% in price, from $11 to $434 for a bottle of 100 2-mg tablets.
- Doxycycline hyclate, an antibiotic used to treat a variety of infections, increased 8,281% in price for a bottle of 500 100-mg tablets (from $20 to $1,849).
- Glycopyrrolate, used to prevent irregular heartbeats during surgery, increased 2,728% in price for a box of 10 0.2-mg/mL, 20-mL vials (from $65 to $1,277).

It doesn't appear that any of the 10 drugs cited in the letters are marketed by only one company, so competition should keep prices from breaking through the roof. But in some instances, that competition is limited. Albuterol sulfate is sold by Mylan and Mutual Pharmaceuticals. Doxycycline hyclate is sold by 10 companies, with three representing most of the market share. West-Ward, Inc., dominates the market for glycopyrrolate.

Mylan, Teva, and Lannett Company, Inc., are among the companies that received the Cummings/Sanders letter. The first two did not respond to a query asking for a response. In its 2013 annual report, Lannett said: "Gross profit improved considerably to $57 million from $39 million. As a percent of net sales, gross margin rose to 38% from 32%, with the increase primarily due to favorable sales mix, price increases, and enhanced manufacturing efficiencies." Asked about the extent of product price increases, spokesman Robert Jaffe says, "Lannett's management respectfully declines to be interviewed."

Why the Price Hikes?

A number of factors can cause a spike in a generic price, justifiable or perhaps not. There are also reasons why drug prices won't drop. A number of mega-consolidations have taken place in the industry over the past few years. One by one, generic companies are disappearing. Competition in each category is diminishing. Earlier this year, Mylan acquired Agila Specialties Private Ltd., giving Mylan a strong hold on the generic injectables market. In that instance, the FDA forced Mylan to divest drugs in a number of categories before it approved the acquisition. For example, Mylan divested etomidate injection, ganciclovir injection, and some other injectables to JHP Pharmaceuticals. Earlier this year, Par Pharmaceutical Companies, Inc., acquired JHP. Valeant Pharmaceuticals International, Inc., is trying to acquire Allergan, Inc., and promises, if successful, to put a plug in its research pipeline. Teva acquired Cephalon, Inc., in 2012. Also in 2012, Valeant bought Ortho Dermatologics, Inc., from Johnson & Johnson and Dermik Laboratories, Inc., from Sanofi.

New products are not entering the market as quickly as had been hoped in the wake of GDUFA passage. And when they do enter the market, it is after the manufacturer has spent more in development and regulatory costs than might otherwise have been necessary. The GDUFA was supposed to pave the way for eliminating ANDA approval backlogs by mandating, for the first time, that generic suppliers pay "user fees" to the FDA. In return, the agency committed to approving ANDAs—submitted when a generic company wants to sell a copy of a patented pharmaceutical—according to specified time frames. The fees amount to about $300 million a year. The GDUFA required the FDA to publish five guidance documents that lay out how the agency planned to meet the approval deadlines in its GDUFA "commitment letter." For example, the FDA has committed to review and act on 90% of original ANDA submissions within 10 months from the date of submission in year 5 of the program, which begins on October 1, 2016.

Of course, generic companies themselves are responsible for many delays. They fight like Hatfields and McCoys over whether one or the other should have its ANDA approved, whether as the "first-time" generic in a category or as a new competitor to an existing generic. One example is Apotex Corporation's filing of a citizen petition with the FDA in January 2014 to block Forest Laboratories' generic version of Apotex's Namenda XR (memantine hydrochloride extended release capsules). The Apotex drug was approved in June 2010 and first became available in June 2013. Apotex argued that since its drug only became available in June 2013, it would have been impossible, time-wise, for Forest to conduct the required bioequivalence studies. The FDA rejected the petition on June 12, 2014. Ross Maclean, PhD, Senior Vice President for Scientific and Regulatory Affairs at Apotex, did not return a call asking for comment.

In filing its citizen petition, Apotex was trying to prevent Forest from claiming 180-day market exclusivity, which has price implications, too. (Forest disappeared last February when it was swallowed by Actavis). The 180-day period was put into law in 1984 as part of the Hatch-Waxman Drug Price Competition and Patent Term Restoration Act of 1984. It is supposed to function as an incentive for a generic company to be the first to submit an ANDA for a brand-name drug coming off patent. Since GDUFA was signed into law, at least 19 first applicants have forfeited 180-day exclusivity because they failed to get timely FDA approval, according to the GPhA. Typically, once a paragraph IV ANDA is filed, a 30-month clock starts if the brand-name company challenges the generic company's right to sell a product because of patent infringement. If the FDA fails to review an ANDA prior to the expiration of the patent being challenged, the 180-day exclusivity may be lost. With the patent or patents expired, any generic company can sell a copy of that brand-name drug. So that 180-day "incentive" is not much of an incentive these days.

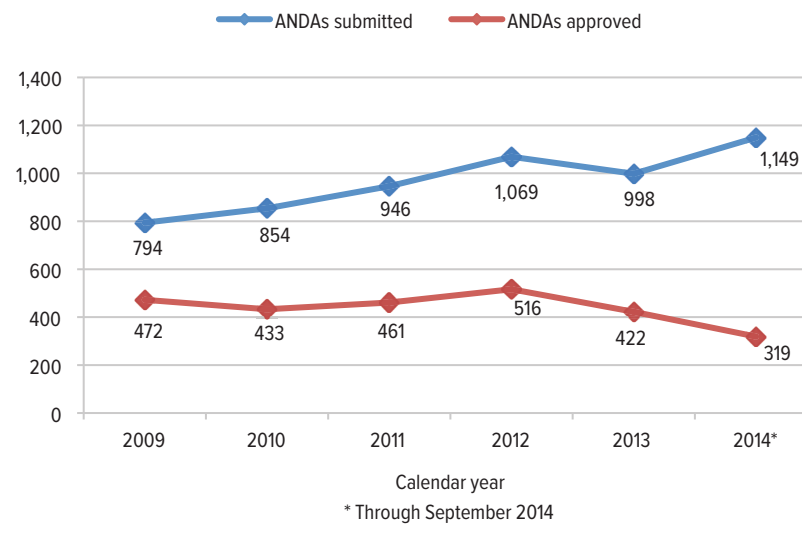
The confusion over exclusivity can affect pricing in opposite directions. Michael D. Shumsky, an attorney for Kirkland and Ellis, LLP, and an outside counsel to Teva, explains that if a first generic applicant believes it is entitled to exclusivity, it typically will produce enough product to satisfy the entire market. But it could wind up with substantial inventories that it will never be able to sell if the FDA subsequently holds that the applicant is not entitled to exclusivity. The resulting losses are then passed on to consumers in the form of higher prices, which undermines the statute's basic goal of lowering prescription drug costs.

The reverse is also true. If a first generic applicant believes that the FDA will find it has forfeited or otherwise lost its exclusivity, it may not prepare sufficient quantities of a product to supply the market—leaving it unable to fulfill consumer demand in the event that the FDA finds the applicant has maintained its eligibility for exclusivity. That likewise increases costs for consumers.

The GDUFA: Promises and Pitfalls

The 180-day exclusivity period and the FDA's policies for granting it were among the topics on the agenda of the FDA's September 17 meeting. Also up for discussion were the five draft guidance documents the agency has issued as follow-ups to its GDUFA commitment letter. At the time of the GDUFA's passage in 2012, more than 2,700 generic applications were awaiting FDA approval, and the average approval time for an application stretched beyond 30 months—five times longer than the statutory six-month review time called for by the Hatch-Waxman Act. That backlog had been reduced to about 2,100 when Greg Giba announced his departure as director of the FDA's Office of Generic Drugs (OGD) in March 2013. Giba, whose appointment had been announced only the previous July, quit because a reorganization left him with less resources than he felt he needed. A new permanent director has not been appointed.

Figure 1 Abbreviated New Drug Applications Submitted to and Approved by the FDA



But the ANDA backlog (Figure 1) remains a cause célèbre for the generics industry. So does its impact on company costs, which affects product pricing. The FDA has said several times that one objective of GDUFA was to reduce costs to generic manufacturers. But Jump, of Cornerstone Regulatory, says that costs for industry have increased since GDUFA's passage:

> In fact, since the law has gone into effect, user fees have been instituted, requirements for the production and submission of three registration batches for each product strength, and the refusal to accept stability data with less than six months of stability data have all increased the costs to industry. The potential for earlier approvals, which has not been seen to date, can at best only potentially increase industry revenue, but it cannot decrease development costs.

The September 17 meeting, held as the October 1, 2014, start of the first iteration of GDUFA timetables was looming, touched on five guidance documents the FDA had issued in draft form. They are supposed to give the industry a clearer idea of what the FDA expects in an ANDA in various areas. The five guidance documents are:

- ANDA Submissions—Content and Format of ANDAs[4]
- ANDA Submissions—Refuse to Receive for Lack of Proper Justification of Impurity Limits[5]
- ANDA Submissions—Amendments and Easily Correctable Deficiencies Under GDUFA[6]
- ANDA Submissions—Prior Approval Supplements Under GDUFA[7]
- Controlled Correspondence Related to Generic Drug Development[8]

Most of these draft guidances were published this past summer. They are too mind-numbingly arcane to discuss here. Suffice it to say that the response to most of the draft guidance documents has not been particularly positive. With regard to

"Content and Format of ANDAs," Jump complains, for example, that his clients "are dismayed" that the FDA is requesting that the cover letter contain the same information contained in the common technical document (CTD) and the 356h form. This is an unnecessary duplication of information. "Repeating the same information in multiple places only increases the chances that inadvertent mistakes can be made," Jump states. "These inadvertent mistakes are frequently the cause of deficiency comments from the agency asking which information is correct." The CTD is the international format for what should be included in the ANDA. For instance, manufacturing site and contact information are requested in the FDA 356h form and specific sections defined within the ANDA. Now companies will have to include that same data in a third place, the cover letter, increasing the chances that there may be inadvertent discrepancies among the three. An FDA reviewer might kick back the application for that reason.

The problem these days is that reviewers aren't "kicking out" approved applications. "I agree there are some major issues at the Office of Generic Drugs," says Bob Pollock, Senior Advisor and Outside Director to the board of Lachman Consultants. Pollock, who left the FDA in 1994 as Acting Deputy Director of the OGD, writes a blog on the Lachman website. "One thing that surprises me is that there is more emphasis on process, policy, and procedure. They also need more attention to moving the freight. Folks in the industry are scratching their heads, wondering when things are going to improve."

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